

AWARD NUMBER: W81XWH-14-2-0159

TITLE: Prostate Cancer Clinical Consortium Clinical Research Site: Targeted Therapies

PRINCIPAL INVESTIGATOR: David Nanus

CONTRACTING ORGANIZATION: Weill Medical College of Cornell University
New York, NY 10065

REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188		
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1. REPORT DATE October 2017		2. REPORT TYPE Annual		3. DATES COVERED 09/30/2016 – 09/29/2017	
4. TITLE AND SUBTITLE Prostate Cancer Clinical Consortium Clinical Research Site: Targeted Therapies			5a. CONTRACT NUMBER		
			5b. GRANT NUMBER W81XWH-14-2-0159		
			5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S) David Nanus, M.D. E-Mail: dnanus@med.cornell.edu			5d. PROJECT NUMBER		
			5e. TASK NUMBER		
			5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Weill Medical College of Cornell University 1300 York Avenue, Box 89 New York, NY 10065-4805			8. PERFORMING ORGANIZATION REPORT		
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSOR/MONITOR'S ACRONYM(S)		
			11. SPONSOR/MONITOR'S REPORT NUMBER(S)		
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The Weill Cornell Medical College Prostate Cancer Research Program (WCMC-PCRP) is a Clinical Research Site of the Prostate Cancer Clinical Trials Consortium (PCCTC). The purpose of the research is to lead and participate in Consortium therapeutic and correlative science research protocols. Specifically, our aims are to impact prostate cancer care and outcomes through the development and study of novel targeted therapeutics, discovery of mechanisms of therapy resistance/sensitivity, identification of new therapeutic targets through high quality genomic analyses, providing access to the highest quality PC tissue specimens, and development of molecular imaging techniques with direct relevance to targeted therapies. Our overarching goal is to more effectively bring novel agents and new biomarker driven trials directly to patients.					
15. SUBJECT TERMS Nothing listed					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER 28	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

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1. INTRODUCTION:

The Weill Cornell Medical College Prostate Cancer Research Program (WCMC-PCRP) is a Clinical Research Site of the Prostate Cancer Clinical Trials Consortium (PCCTC). The purpose of the research is to lead and participate in Consortium therapeutic and correlative science research protocols. Specifically, our aims are to impact prostate cancer care and outcomes through the development and study of novel targeted therapeutics, discovery of mechanisms of therapy resistance/sensitivity, identification of new therapeutic targets through high quality genomic analyses, providing access to the highest quality PC tissue specimens, and development of molecular imaging techniques with direct relevance to targeted therapies. Our overarching goal is to more effectively bring novel agents and new biomarker driven trials directly to patients

2. KEYWORDS:

aurora kinase A, clinical trials, circulating tumor cells, monoclonal antibody, neuroendocrine prostate cancer, next-generation sequencing, prostate cancer, Prostate Cancer Clinical Trials Consortium, prostate specific membrane antigen, translational research program,

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain

prior written approval from the USAMRAA Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

SOW Major Task 1: Adhere to performance metrics defined by Coordinating Center

SOW Major Task 2: Full participation in the consortium as a member of the Clinical Consortium Committee/Scientific Oversight Committee

SOW Major Task 3: Regulatory review, Clinical trial startup

SOW Major Task 4: Propose clinical trials to Consortium

SOW Major Task 5: Interim data analysis

SOW Major Task 6: Open other Consortium sponsored Clinical Trials at WCMC

SOW Major Task 7: Clinical trial performance

SOW Major Task 8: Investigator analysis, reporting of initial data

SOW Major Task 9: Analysis and reporting of final data

What was accomplished under these goals?

SOW Major Task 1: Adhere to performance metrics defined by Coordinating Center

Subtask 1. Accrue at least 25 patients per year to PCCTC trials: Fifty-six (56) patients have enrolled to the 9 currently active PCCTC protocols in this reporting period. Total enrollment number for the below PCCTC trials are updated below.

Study Title	Year 1	Year 2	Year 3
A Phase II Trial of the Aurora Kinase A Inhibitor in Patients with mCRPC and NEPC [c12-105]	6	2	
Randomized Phase II 3-Arm Study of Abiraterone, Abiraterone Plus Degarelix, and Degarelix Alone for Patients with a Rising PSA Following Radical Prostatectomy [c11-092]	3	3	0*
Randomized Phase II Trial of Abiraterone With or Without Cabazitaxel in Treatment of mCRPC [c12-108]	1	2	1
Phase II trial assessing pain efficacy with Radium-223 in symptomatic mCRPC [c13-124]	5	6	5*
Circulating Molecular Predictors of Chemotherapy and Novel Hormonal Therapy Benefit in mCRPC [c14-144]	1	18	1
Phase Ib/II Randomised Study of BI 836845 + Enzalutamide versus Enzalutamide alone in mCRPC [c14-147]		0	2

Phase I Trial to Evaluate Safety and Immunogenicity of INO-5150 Alone or in Combination with INO-9012 in Men with Biochemically Relapsed PC [c15-158]		2	0*
Phase II Trial of Pembrolizumab (MK-3475) in Subjects with mCRPC Previously Treated with Chemotherapy [c16-184]			0
Phase I Trial of ARN-509 plus Abiraterone, Docetaxel, and Prednisone in Patients with mCRPC (c15-163)			6
A Phase I/II Study of Immu-132 (hRS7-SN38 Antibody Drug Conjugate) in Patients with Epithelial Cancer [c17-193]			3
Phase I dose-escalation study of fractionated dose 177Lu-PSMA-617 for progressive mCRPC [c17-199]			17
Phase 3 Study of 99mTc-MIP-1404 SPECT/CT Imaging to Detect Clinically Significant Prostate Cancer in Men with Biopsy Proven Low-Grade Prostate Cancer who are Candidates for Active Surveillance (proSPECT-AS) [c16-105]		3	21
Total:	16	36	56

*Closed to enrollment during reporting period

Patient Sample Accrual

PCCTC LOI# c12-105: 60 pre-treatment tissue biopsies, and >100 serial plasmas samples were processed.

PCCTC 12-107 (which was closed to new patient accrual before 9/30/14 but circulating tumor cell (CTC) samples continued to be received by WCM), over 500 CTC samples were analyzed for drug target engagement.

PCCTC c14-144: 120 CTC samples have been analyzed by digital droplet polymerase chain reaction (ddPCR) for androgen receptor variants.

Subtask 2. Accrue at least 5% of patients from disproportionately affected populations per year

Eleven of f

ifty-six enrolled patients were from disproportionately affected populations (19.64%)

Demographic	African American	White NH	White H	Asian	Other	Total Subjects in Year
Year 3 9/30/16- 9/29/17	7	45	1	2	1	56
	12.50%	80.36%	1.79%	3.57%	1.79%	

Subtask 3. Propose ≥ 2 clinical trials per year or 6 trials over 3 years for consideration by the consortium, which may include biomarker studies:

The table below displays all the clinical trials within the consortium that we are the PIs/lead investigators. In addition to the activated studies below, we have a number of protocols in various stages of start-up.

Study Title	WCM PI or Collaborator
A Phase II Trial of the Aurora Kinase A Inhibitor in Patients with mCRPC and NEPC [c12-105]	PI
Circulating Molecular Predictors of Chemotherapy and Novel Hormonal Therapy Benefit in mCRPC [c14-144]	PI
Phase Ib/II Randomised Study of BI 836845 + Enzalutamide versus Enzalutamide alone in mCRPC [c14-147]	PI
Phase I Trial of ARN-509 plus Abiraterone, Docetaxel, and Prednisone in Patients with mCRPC (c15-163)	PI
A Phase I/II Study of Immu-132 (hRS7-SN38 Antibody Drug Conjugate) in Patients with Epithelial Cancer [c17-193]	PI
Phase I dose-escalation study of fractionated dose ¹⁷⁷ Lu-PSMA-617 for progressive mCRPC [c17-199]	PI

Subtask 4. Participate as a Clinical Research Site in >6 trials initiated by other sites: We have opened 6 trials to date initiated by other sites, including one in which we are co-investigators on a PCF Challenge Award.

Study Title	WCM PI or Collaborator
Randomized Phase II 3-Arm Study of Abiraterone, Abiraterone Plus Degarelix, and Degarelix Alone for Patients with a Rising PSA Following Radical Prostatectomy [c11-092]	Collaborator
Randomized Phase II Trial of Abiraterone With or Without Cabazitaxel in Treatment of mCRPC [c12-108]	Collaborator
Phase II trial assessing pain efficacy with Radium-223 in symptomatic mCRPC [c13-124]	Collaborator
Phase I Trial to Evaluate Safety and Immunogenicity of INO-5150 Alone or in Combination with INO-9012 in Men with Biochemically Relapsed PC [c15-158]	Collaborator
Phase II Trial of Pembrolizumab (MK-3475) in Subjects with mCRPC Previously Treated with Chemotherapy [c16-184]	Collaborator

Phase 3 Study of 99mTc-MIP-1404 SPECT/CT Imaging to Detect Clinically Significant Prostate Cancer in Men with Biopsy Proven Low-Grade Prostate Cancer who are Candidates for Active Surveillance (proSPECT-AS) [c16-105]	Collaborator
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Additional protocols are in various stages of completion and/or start up include: 1) A Salvage Trial of AR Inhibition with ADT and ARN-509 with Docetaxel followed by Radiation Therapy in Men with PSA Recurrent PC after Radical Prostatectomy (STARTAR) (c16-180); 2) PC Outcomes: An International Registry to Improve Outcomes in Men with Advanced PC (IRONMAN) (c16-170); 3) ARN-509+Abiraterone acetate+Leuprolide with Stereotactic, Ultra-Hypofractionated Radiation (AASUR) in Very High Risk PC: A Single Arm, Phase II Study (c15-164); and 4) A Randomized Phase II trial of Abiraterone, Olaparib, or Abiraterone + Olaparib in Patients with Metastatic CRPC with DNA Repair Defects (BRCAAway) (c16-168).

SOW Major Task 2: Full participation in the consortium as a member of the Clinical Consortium Committee/Scientific Oversight Committee

Subtask 1. Participate in ≥ 1 PCCTC committee: Dr. Nanus is a member of the Scientific Oversight Committee and Dr. Tagawa serves as an Alternate.

Subtask 2. Attend all face-to-face meetings of the PCCTC: Dr. Nanus, Dr. Tagawa and/or Dr. Beltran attended all face-to-face meetings of the PCCTC.

Subtask 3. Participate in scheduled consortium conference calls: Dr. Nanus and/or Dr. Tagawa have participated in all PCCTC scheduled consortium conference calls. WCM investigators presented on the conference call in December 2015 and March 2017. .

Subtask 4. Participate in review meetings/evaluation by the External Advisory Board (EAB): No EAB meetings have yet occurred.

Subtask 5. Compliance with the operations manual of the Consortium: We have been compliant.

SOW Major Task 3: Regulatory review, Clinical trial startup.

Subtasks 1 thru 4 have each been completed (Submission of protocols for scientific (WCMC Protocol Review Committee) and WCMC Institutional Review Board (WCMC Clinical and Translational Science Center review if indicated); Completion of contractual agreements between Coordinating Center and WCMC; Clinical trial approval at WCMC; and Site initiation visits). Additional trials in various stages of regulatory review.

SOW Major Task 4: Propose clinical trials to Consortium

Subtask 1. Propose new therapeutic trial to Coordinating Center and other Consortium sites: See above (Major Task 1, Subtask 3).

Subtasks 2- thru 7. Subtasks 2 thru 7 are partially accomplished and ongoing as specifically related to each WCMC initiated protocol (Submission of protocol for scientific review; start up at additional sites; clinical trial initiation at WCMC and other collaborating sites; Screen, enroll, and treat subjects; ongoing communication with study sites; Ongoing communication with IRB, DSMB, FDA).

SOW Major Task 5: Interim data analysis

Data for PCCTC c12-107 (TAXYENERGY, a phase II trial to evaluate benefit of early switch from first-line docetaxel/prednisone to cabazitaxel/prednisone and the opposite sequence, exploring molecular markers and mechanisms of taxane resistance in men with metastatic CRPC who have not received prior chemotherapy) was closed to new patient accrual before 9/30/14 but CTC samples were analyzed at WCMC. CTC data has and continues to be analyzed (see below).

SOW Major Task 6: Open other Consortium sponsored Clinical Trials at WCMC

See above in Major Task 1 for details.

SOW Major Task 7: Clinical trial performance

See above in Major Task 1 for details.

SOW Major Task 8: Investigator analysis, reporting of initial data

Subtask 1. Verification of data

This milestone has been reached for c12-107 and c12-105 (A Phase II Trial of the Aurora Kinase A Inhibitor in Patients with mCRPC and NEPC) with data published or submitted for publication (see below).

Subtask 2. Analysis of initial data

This milestone has been reached for c12-107 and c12-105 with data published or submitted for publication. Correlative data continues to be analyzed on c12-107.

Protocol c14-147 (Phase Ib/II Randomised Study of BI 836845 + Enzalutamide versus Enzalutamide alone in mCRPC) is closed to accrual and data analysis has begun.

Subtask 3. Reporting of initial data

Over the past reporting period, Dr. Beltran presented data for c12-105 (A Phase II Trial of the Aurora Kinase A Inhibitor in Patients with mCRPC and NEPC) at the ESMO annual meeting in October, 2016.

Beltran H, Danila D, Montgomery B, Szmulewitz R, Vaishampayan U, Armstrong A, Hoimes C, Stein M,

Pinski J, Scher H, Puca L, Bareja R, Wong W, Rubin MA, Mosquera JM, Sboner A, Oromendia C, Nanus DM, Ballman K, Tagawa ST, A phase 2 study of the aurora kinase A inhibitor alisertib for patients with neuroendocrine prostate cancer (NEPC), Oral Abstract Presentation (Late Breaking), ESMO Annual Meeting, Copenhagen, Denmark, Oct 2016

SOW Major Task 9: Analysis and reporting of final data

c12-107: A manuscript describing this study has been published in the *Journal of Clinical Oncology*.

(Antonarakis ES, Tagawa ST, Galletti G, Worroll D, Ballman K, Vanhuyse M, Sonpavde G, North S, Albany C, Tsao C-K, Stewart J, Zaher A, Szatrowski T, Zhou W, Gjyrezi A, Tasaki S, Portella L, Bai Y, Lannin TB, Suri S, Gruber CN, Pratt ED, Kirby BJ, Eisenberger MA, Nanus DM, Saad F, Giannakakou P. A randomized non-comparative phase II trial of early switch from docetaxel to cabazitaxel or vice versa, with integrated biomarker analysis, in men with chemotherapy-naïve metastatic castration-resistant prostate cancer. *J Clin Onc* 2017;35:3181-3188).

A second manuscript describing a more detailed bio-marker analysis of samples from c12-107 is in preparation.

c12-105: A manuscript describing these data is in review at the journal *Cancer Discovery*. (Beltran H, Oromendia C, Danila D, Montgomery B, Hoimes C, Szmulewitz R, Vaishampayan U, Armstrong AJ, Stein M, Pinski J, Scher HI, Mosquera JM, Sailer V, Bareja R, Romanel A, Gumpen N, Sboner A, Dardenne E, Puca L, Rubin MA, Prandi D, Rickman D, Nanus DM, Demichelis F, Ballman K, Tagawa ST. A phase II study of the aurora kinase A inhibitor alisertib for patients with neuroendocrine prostate cancer).

What opportunities for training and professional development has the project provided?

Dr. Beltran led a multi-institutional clinical trial (PCCTC LOI# c12-105) as PI, communicating with other sites, and presented these trial results at the ESMO Annual Meeting. She also participates in PCCTC group meetings and trials. She was recently appointed the GU correlative science committee chair for the Alliance cooperative group.

Dr. Beltran and Dr. Tagawa have presented during the PCCTC Investigator teleconferences for WCM.

Dr. Tagawa has presented at the annual ASCO meeting and attended the annual ESMO conference.

How were the results disseminated to communities of interest?

Press releases from WCMC have accompanied publications of our data.

What do you plan to do during the next reporting period to accomplish the goals?

We will continue to recruit to currently open consortium studies, as well as open other clinical trials being offered through the consortium. We expect increased enrollment to consortium studies in the upcoming year. We also currently have multiple WCMC-initiated studies in development, which will be offered to other sites in the consortium in the upcoming year.

4. IMPACT:

Nothing to Report

5. CHANGES/PROBLEMS:

Nothing to Report

6. PRODUCTS:

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS What individuals have worked on the project?

Personnel	Role	Percent Effort
David Nanus	Principal Investigator	10%
Mark Rubin	Co-Investigator	3%
Scott Tagawa	Co-Investigator	3%
Himisha Beltran	Co-Investigator	3%
Jyothi Sreekumar	Clinical Research Coordinator	45%
Hoda Bashir	Research Nurse	45%
Aileen Lee	Data Coordinator	67%

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

David Nanus:

Dr. Nanus requested a no-cost extension on this DOD grant W81XWH-14-2-0159 which was approved. The new end date for this project is 9/29/18.

Dr. Nanus received the following new funding in the past year:

P50 CA211024 Specialized Programs of Research Excellence (SPORE) (PI: Rubin / Beltran)

Weill Cornell Medicine (WCM) SPORE in Prostate Cancer

Developmental Research Program (DRP): (Co-Director: Nanus)

National Cancer Institute

Effort: 0.3 calendar (DRP)

Grants Officer: Andrew Hruszkewycz; email: hruzke@mail.nih.gov; phone: 240.276.5687

Performance Period: 07/01/2017-06/30/2022

\$1,419,585 total DC first year (DRP first year DC)

Goals/Aims: The Developmental Research Program (DRP) will act as an incubator for high-risk/high-gain and novel collaborative projects within the Weill Cornell Medicine (WCM) SPORE in Prostate Cancer (PCa). Each DRP project will require one-to-two years of development time and funds to facilitate compelling preliminary data. To this end, the WCM SPORE will establish a DRP that will address 1) develop infrastructure to solicit competitive developmental projects across the Weill Cornell and Columbia University campuses, 2) facilitate evaluation of proposals for the DRP, and 3) implement procedures for a developmental project to replace an existing major SPORE Project.

Roles: Developmental Research Program (DRP) Co-Director

Dr. Nanus received the following projects end in the past year:

2014 Movember-PCF GTSC Award (Armstrong)

Title: Development of Circulating Molecular Predictors of Chemotherapy and Novel Hormonal Therapy Benefit in Men with Metastatic Castration Resistant Prostate Cancer (mCRPC)

Effort: 0.6 calendar

Supporting Agency: Prostate Cancer Foundation

Contact Person: Howard R. Soule, phone: 310-370-4598

Duration: 8/01/2014 – 07/31/2017 (NCE)

Direct Costs (current year):

Project Goals/Aims: This project aims 1. Assessment of a CRPC molecular taxonomy based on circulating tumor cell (CTC) molecular profiles in men prior to abiraterone acetate (AA) or enzalutamide therapy and, 2. To describe treatment-emergent CRPC genotypes during AA, enzalutamide, and taxane-based therapy using longitudinal CTC and circulating biomarkers.

Role: Co-Principal Investigator

Scott Tagawa:

Dr. Tagawa requested an additional no-cost extension on his DOD grant W81XWH-09-1-059, which was approved. The new end date for this project is 8/16/18. Dr. Tagawa received the following new funding in the past year:

PCF Challenge Award (Tagawa/Bander/Vallabhajosula)

Title: Optimization of prostate-specific membrane antigen-targeted radiation

Time Commitment: 1.2 calendar

Supporting Agency: Prostate Cancer Foundation

Grants Officer: Howard R. Soule, Prostate Cancer Foundation; email: hsoule@pcf.org

Performance Period: 10/1/2017– 09/30/2019

Level of Funding:

Goals: To optimize the early-stage development of PSMA-targeted ^{177}Lu and set the stage for continued development of PSMA-targeted alpha emitters. Aims: 1. To optimize dose and schedule of PSMA-targeted ^{177}Lu , we will prospectively study the most commonly used PSMA small molecule and optimize therapy with dose-fractionation. 2. To prospectively and retrospectively assess the optimal patient population to receive ^{177}Lu -radiolabeled PSMA agents. 3. To complete a phase I dose-escalation study of ^{225}Ac -J591 with the primary endpoint of dose-limiting toxicity and MTD determination followed by expansion at the recommended phase 2 dose cohort to gain additional safety experience as well as preliminary efficacy data.

Movember-PCF Challenge Award (Lang/Scher/Dehm/Tagawa)

Title: Therapeutic Targeting of AR Variant Prostate Cancer with a Novel Antibody Drug Conjugate

Time Commitment: 1.2 calendar

Supporting Agency: Prostate Cancer Foundation

Grants Officer: Howard R. Soule, Prostate Cancer Foundation; email: hsoule@pcf.org

Performance Period: 08/31/2017– 08/31/2019

Level of Funding:

Goals/Aims: To evaluate and validate Trop2 biomarkers, to treat patients with IMMU-132, and to evaluate predictive and pharmacodynamic biomarker assays of response and resistance to IMMU-132.

Role: Co-Principal Investigator

WCMC SPORE Initiative (Tagawa/Bander/Vallabhajosula)

Title: PSMA-targeted alpha-radioimmunotherapy with ^{225}Ac -J591

Time Commitment: 0 calendar

Supporting Agency: Weill Cornell Medicine Meyer Cancer Center

Contracting Officer: Kate Carbonell, Research Program Manager, WCM, 646-962-6165, kac2051@med.cornell.edu

Performance Period: 04/1/2017 – 03/31/2018

Level of Funding:

Project Goals/Aims: Aims: 1) to complete preclinical studies and obtain IND for ^{225}Ac -J591 and 2) to initiate a phase I dose-escalation study of single-dose ^{225}Ac -J591 in men with metastatic castration-resistant prostate cancer

Role: Co-Principal Investigator

Dr. Tagawa had the following projects end in the past year:

NYS DOH Research Grant (Tagawa/Giannakakou)

Title: Molecular Determinants of Response and Resistance to Taxanes and Androgen Deprivation Therapy in Castration-Resistant Prostate Cancer

Supporting Agency: New York State Department of Health

Contracting Officer: N/A

Performance Period: 11/01/2015- 01/31/2017

Level of Funding:

Project Goals/Aims: This project aims to perform molecular profiling of PC-patient derived CTCs.

Role: Co-Principal Investigator

Mark Rubin:

Dr. Rubin received the following new funding in the past year:

P50 CA211024 Specialized Programs of Research Excellence (SPORE) (PI: Rubin / Beltran)

Title: Weill Cornell Medicine (WCM) SPORE in Prostate Cancer

Admin Core: (Project Leader: Rubin)

Project 3: Towards understanding prostate cancer heterogeneity (Project Leaders: Rubin / Shen / Tomlins)

National Cancer Institute

Effort: 1.2 calendar (Admin Core); 1.5 calendar (Project 3) *

Grants Officer: Andrew Hruszkewycz; email: hruszkea@mail.nih.gov; phone: 240.276.5687

Performance Period: 07/01/2017-06/30/2022

Level of Funding: total DC first year (: Admin Core first year DC); : Project 3 first year DC)

Goals/Aims Admin Core: The Administrative Core will provide leadership and organization, administrative and financial oversight, including the coordination of scientific oversight, to ensure the WCM SPORE in Prostate Cancer operates successfully. As SPORE PI and the Administrative Core Director, Mark A. Rubin, MD, will ensure Project Co- Leaders advance their research along the translational pipeline, share information with one another including the greater research community, have access to the resources from the two scientific Cores, obtain feedback from the Internal and External Advisory Boards (IAB and EAB), and foster developmental research and the careers of prostate cancer researchers.

Goals/Aims Project 3: The goal of this project is will identify molecular mediators of progression to CRPC, inform on the actual impact of multifocality/heterogeneity and determine the optimum approach to identify the true “index” focus at prostatectomy.

Roles: Principal Investigator; Admin Core Leader; Project 3 Co-Leader

Dr. Rubin had the following projects end in the past year:

Prostate Cancer Foundation, Challenge Award (PI Rubin)

Title: Integrative Genomics of Prostate Cancer Progression

Effort: 1.8 calendar

Prostate Cancer Foundation

Grants Officer: Audrey Gardner; email: agardner@pdf.org; phone: 310-570-4792

Performance Period: 10/1/15-9/30/17

Level of Funding:

Project Goals/Aims: Project Aims: Aim 1. Collect and histologically characterize original primary ADT-naïve specimens from patients enrolled in the CRPC 500 trial. Aim 2. Determine the molecular landscape of multiple tumor foci from the original ADT-naïve CRPC 500 specimens through DNA and RNA sequencing. Aim 3: Identify molecular mediators of PCa progression and track the progressing clone through an integrative molecular profiling analysis of paired primary ADT-naïve and CRPC specimens. Overlap: None

RFA#1410200115 (PI Rubin)

Title: Prostate Cancer Research

Effort: 0.12 calendar

New York State Dept. of Health

Grants Officer: Janet Roach; E-mail: jmr04@health.ny.gov; Phone: 518-474-1222

Performance Period: 11/1/15-1/31/17

Level of Funding:

Project Goals/Aims: This RFA is to support NYS-based research institutions to conduct hypothesis development research in prostate cancer. This funding is intended to offer investigators opportunities to explore innovative, untested hypotheses, the results of which could provide the scientific rationale upon which new hypotheses or initial proofs-of-principle of innovative hypotheses can be generated.

Overlap: None

R01 CA116337 (PI Rubin)

Title: Molecular Signatures of Lethal and Indolent Prostate Cancer

National Cancer Institute (NIH)

Grants Officer: Michael Zarkin; e-mail: zarkinm@mail.nih.gov

Performance Period: 07/23/2012-05/31/2017

Level of Funding:

The goals of this project are to define mutations and somatic copy number alterations associated with the emergence of lethal prostate cancer and determine their functional activity.

Role: Principal Investigator

Himisha Beltran:

Dr. Beltran requested and received approval for a no-cost extension on her Department of Defense Physician Research Training Award (W81XWH-13-1-0275), "A Changing Landscape of Advanced Prostate Cancer: Understanding mechanisms of Resistance to Potent Hormonal Therapies." The new end date for the project is 9/29/18.

Dr. Beltran received the following new funding in the past year:

P50 CA211024 Specialized Programs of Research Excellence (SPORE) (PI: Rubin / Beltran)

Title: Weill Cornell Medicine (WCM) SPORE in Prostate Cancer

Project 1: Non-invasive clinical assay for early detection of treatment resistance in patients with metastatic prostate cancer (Project Leader: Beltran)

Project 2: Targeting N-MYC and EZH2-Driven Castrate Resistant Prostate Cancer (Project Leaders: Rickman / Beltran)

National Cancer Institute

Effort: 1.2 calendar (Project 1); 1.2 calendar (Project 2) *

Grants Officer: Andrew Hruszkewycz; email: hruzkeaa@mail.nih.gov; phone: 240.276.5687

Performance Period: 07/01/2017-06/30/2022

Level of Funding: total DC first year Project 1 first year DC); : Project 2 first year DC)

Goals/Aims Project 1: The goals of this project are to determine tumor dynamics and the clinical impact

of circulating alterations in predicting response to AR-directed therapy and define the spectrum of circulating DNA alterations in patients with metastatic CRPC.

Goals/Aims Project 2: The goal of this project is to develop more effective targeting strategies for a biomarker-selected subgroup of late stage CRPC driven by N-Myc and less dependent on the AR.

Roles: Co-Principal Investigator; Project 1 Leader; Project 2 Co-Leader

SU2C Colorectal Cancer Dream Team (PI: Cantley)

Title: Targeting Foundational Drivers in Colorectal Cancer

Effort: 0.60 calendar

Stand Up To Cancer (SU2C)/AACR

Grant Officer: N/A

Performance Period: 07/01/2017–06/30/2020

Level of Funding:

Project Goals/Aims: This project proposes to perform clinical trials to test four different novel therapies that we have developed in terminal ill colorectal cancer patients through a multiple-institution collaboration. The goal of this study is to test if these drugs can cure colorectal cancers or prolong life of colorectal cancer patients.

Role: Co-Investigator

W81XWH-17-1-0653 (PIs: Rickman/Beltran) Impact Award

Title: Temporal Evolution of N-Myc and Early Targeting of the Neuroendocrine Phenotype in Prostate Cancer

Effort: 2.40 calendar months

Department of Defense

Grant Officer: Joshua D. McKean, Grant Specialist, 301-619-9656, e-mail: joshua.d.mckean3.civ@mail.mil

Performance Period: 09/30/2017–09/29/2020

Level of Funding:

Goals/Aims: Aim 1. To assess the timing of N-Myc activation in patients and define how N-Myc and NEPC signaling impacts prognosis, Aim 2. To assess the impact of timing of N-Myc expression on the development of castration resistance and the NEPC phenotype, Aim 3. To evaluate the influence of N-Myc timing on response to NEPC directed therapeutics.

Role: Principal Investigator

2017 PCF Challenge Award (PI: Tagawa)

Title: Optimization of prostate-specific membrane antigen-targeted radiation

Effort: 0.6 calendar

Prostate Cancer Foundation

Grants Officer: Howard Soule; phone: 310-570-4596

Performance Period: 09/01/2017– 08/31/2019

Level of Funding:

Goals/Aims: Optimize the early-stage development of PSMA-targeted ¹⁷⁷Lu, set the stage for continued development of PSMA-targeted alpha emitters, and initiate correlative research into the potential immune effects of this approach.

Role: Co-Investigator

Dr. Beltran had the following projects end in the past year:

R01 CA116337 (PI Rubin)

Title: Molecular Signatures of Lethal and Indolent Prostate Cancer

National Cancer Institute (NIH)

Grants Officer: Michael Zarkin; e-mail: zarkinm@mail.nih.gov

Performance Period: 07/23/2012-05/31/2017

Level of Funding:

The goals of this project are to define mutations and somatic copy number alterations associated with the emergence of lethal prostate cancer and determine their functional activity.

Role: Co-Investigator

Damon Runyon Clinical Investigator Award (PI Beltran)

Title: Using High Throughput Genomic Approaches to Improve Management of Neuroendocrine Prostate Cancer

Effort: 0.6 calendar

Damon Runyon Cancer Research Foundation

Grants Officer: Clare Cahill, tel: 212.455.0520

One Exchange Plaza / 55 Broadway / Suite 302, New York, NY 10006

Performance Period: 07/01/2013 – 06/30/2017 (NCE)

Level of Funding:

The goal of this study is to establish a NEPC-specific genomic profile that distinguishes NEPC from prostate adenocarcinoma (PCA). We will perform targeted deep-exome sequencing of 50 NEPC and PCA to identify NEPC-specific alterations that occur in NEPC and as a function of disease progression. We will also evaluate tumors from patients diagnosed with primary localized disease for early events, and correlate with clinical and pathologic features and outcomes.

Role: Principal Investigator

Sponsored Research Agreement (PI Beltran)

Title: Characterizing AR negative Neuroendocrine Prostate Cancer as a mechanism of resistance to enzalutamide

Astellas Scientific and Medical Affairs, Inc.

Grants Officer: Andree Amelsberg, MD, Astellas Scientific and Medical Affairs, Inc.

Northbrook, IL; phone: (800) 888-7704

Performance Period: 10/14/2013-03/01/2017

Level of Funding:

Project Goals/Aims: To characterize AR negative transformation as one mechanism of tumor resistance to enzalutamide in vitro and in vivo.

Role: Principal Investigator

NY State Department of Health (NYSDOH) Grant (Beltran/Rickman)

Title: Novel Clinically-Relevant Prostate Cancer Models for Co-Clinical Trials

Effort: 0.216 calendar

New York State Department of Health

Grants Officer: Amy M. Yost, Fiscal and Administrative Coordinator, Bureau of Chronic Disease Control, New York State Department of Health, Riverview Center, 150 Broadway, Suite 350, Menands, NY 12204, Phone: 518-474-1222, Email: canserv@health.ny.gov

Performance Period: 11/1/2015-1/31/2017

Level of Funding:

Project Goals/Aims: Aim 1. Characterize the interaction between the epigenome and N-Myc signaling in driving NEPC. Aim 2. Develop novel therapeutic approaches to targeting the epigenome and N-Myc in CRPC and NEPC. Aim 3. Determine the clinical relevance of N-Myc, EZH2, and DNA methylation and response to targeted therapy a prospective clinical cohorts.

Role: Pilot Project Principal Investigator

Overlap: None

Sponsored Research Agreement (Beltran/Rickman/Rubin)

Title: Development of Novel Therapeutics for Treatment of Neuroendocrine Prostate Cancer

Effort: 0.12 calendar

Eli Lilly and Company

Performance Period: 08/07/2015–08/06/2017

Level of Funding:

Project Goals/Aims: Evaluate the activity of the Lilly Aurora kinase inhibitor both in vitro and in vivo. Critical to this proposal is the use of novel preclinical models of NEPC; specifically PDX animal model and biologic/molecular readouts of Aurora-N-Myc activity with a focus on organoid studies.

Aim 1. To determine the impact of the Aurora A inhibitor LSN3199519 on NEPC and Pca in *in vitro* and *in vivo* as monotherapy and in combination with either enzalutamide or carboplatin.

Aim 2. To determine the impact of Lilly Aurora kinase inhibitor and combination therapy with either enzalutamide or carboplatin on reversing NEPC phenotype.

Role: Principal Investigator

What other organizations were involved as partners?

This grant is for the PCCTC consortium, which is a collaboration between all consortium sites.

8. SPECIAL REPORTING REQUIREMENTS:

None

9. APPENDICES:

Copies of manuscript (see Major Task 9).

Randomized, Noncomparative, Phase II Trial of Early Switch From Docetaxel to Cabazitaxel or Vice Versa, With Integrated Biomarker Analysis, in Men With Chemotherapy-Naïve, Metastatic, Castration-Resistant Prostate Cancer

Emmanuel S. Antonarakis, Scott T. Tagawa, Giuseppe Galletti, Daniel Worroll, Karla Ballman, Marie Vanhuyse, Guru Sonpavde, Scott North, Costantine Albany, Che-Kai Tsao, John Stewart, Atef Zaher, Ted Szatrowski, Wei Zhou, Ada Gjyrez, Shinsuke Tasaki, Luigi Portella, Yang Bai, Timothy B. Lannin, Shalu Suri, Conor N. Gruber, Erica D. Pratt, Brian J. Kirby, Mario A. Eisenberger, David M. Nanus, Fred Saad, and Paraskevi Giannakakou on behalf of the TAXYNERGY Investigators

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on June 20, 2017.

E.S.A. and S.T.T. contributed equally to this work. G.G. and D.V.V. contributed equally to this work.

Clinical trial information: NCT01718353.

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0732-183X/17/3599-1/\$20.00

ABSTRACT

Purpose

The TAXYNERGY trial (ClinicalTrials.gov identifier: NCT01718353) evaluated clinical benefit from early taxane switch and circulating tumor cell (CTC) biomarkers to interrogate mechanisms of sensitivity or resistance to taxanes in men with chemotherapy-naïve, metastatic, castration-resistant prostate cancer.

Patients and Methods

Patients were randomly assigned 2:1 to docetaxel or cabazitaxel. Men who did not achieve $\geq 30\%$ prostate-specific antigen (PSA) decline by cycle 4 (C4) switched taxane. The primary clinical endpoint was confirmed $\geq 50\%$ PSA decline versus historical control (TAX327). The primary biomarker endpoint was analysis of post-treatment CTCs to confirm the hypothesis that clinical response was associated with taxane drug-target engagement, evidenced by decreased percent androgen receptor nuclear localization (%ARNL) and increased microtubule bundling.

Results

Sixty-three patients were randomly assigned to docetaxel ($n = 41$) or cabazitaxel ($n = 22$); 44.4% received prior potent androgen receptor-targeted therapy. Overall, 35 patients (55.6%) had confirmed $\geq 50\%$ PSA responses, exceeding the historical control rate of 45.4% (TAX327). Of 61 treated patients, 33 (54.1%) had $\geq 30\%$ PSA declines by C4 and did not switch taxane, 15 patients (24.6%) who did not achieve $\geq 30\%$ PSA declines by C4 switched taxane, and 13 patients (21.3%) discontinued therapy before or at C4. Of patients switching taxane, 46.7% subsequently achieved $\geq 50\%$ PSA decrease. In 26 CTC-evaluable patients, taxane-induced decrease in %ARNL (cycle 1 day 1 v cycle 1 day 8) was associated with a higher rate of $\geq 50\%$ PSA decrease at C4 ($P = .009$). Median composite progression-free survival was 9.1 months (95% CI, 4.9 to 11.7 months); median overall survival was not reached at 14 months. Common grade 3 or 4 adverse events included fatigue (13.1%) and febrile neutropenia (11.5%).

Conclusion

The early taxane switch strategy was associated with improved PSA response rates versus TAX327. Taxane-induced shifts in %ARNL may serve as an early biomarker of clinical benefit in patients treated with taxanes.

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INTRODUCTION

Taxanes are the only class of chemotherapy agents that extend survival in men with advanced prostate cancer.¹⁻⁴ These drugs bind β -tubulin and stabilize cellular microtubules, leading to

inhibition of microtubule-dependent intracellular trafficking and signaling, mitotic arrest, and apoptotic cell death.⁵⁻⁷ Although taxanes are generally considered antimitotic agents, they also inhibit tumor growth via several different mechanisms.⁵ Prostate cancer cells rely heavily on sustained androgen receptor (AR) nuclear

ASSOCIATED CONTENT



Data Supplements

DOI: <https://doi.org/10.1200/JCO.2017.72.4138>

DOI: <https://doi.org/10.1200/JCO.2017.72.4138>

signaling, which drives progression despite androgen-deprivation therapy.⁸ It was recently discovered that AR binds to cellular microtubules via the microtubule-associated motor protein dynein to facilitate its nuclear translocation.⁹ Taxanes can therefore inhibit AR nuclear trafficking via stabilization of microtubules; taxane-induced microtubule stabilization (termed drug-target engagement [DTE]) results in microtubule bundling (MTB), cytoplasmic sequestration of AR, inhibition of AR transcriptional activity, and inhibition of prostate cancer cell growth.^{6,7} In summary, the effectiveness of taxanes in prostate cancer can, at least in part, be attributed to the inhibition of AR signaling.⁹

Overcoming primary (intrinsic) and secondary (acquired) resistance to taxane therapy remains a challenge in prostate cancer treatment, and several different mechanisms of taxane resistance have been proposed (many of which may operate simultaneously).¹⁰⁻¹³ However, because cabazitaxel retains activity in many docetaxel-refractory patients with metastatic castration-resistant prostate cancer (mCRPC), there is evidence to suggest that not all of the same resistance mechanisms apply to all taxanes.¹⁴⁻¹⁷ Therefore, the central clinical hypothesis of this study was that some patients with mCRPC with a suboptimal initial prostate-specific antigen (PSA) decline with their first taxane can subsequently achieve a PSA response by an early switch to a second taxane before clinical progression.

Circulating tumor cells (CTCs) isolated from the blood of patients with mCRPC can serve as a powerful tool to study mechanisms of taxane sensitivity and resistance and can provide a liquid biopsy for serial tumor analysis.^{18,19} Recently developed microfluidic capture techniques enable reliable isolation of CTCs from peripheral blood, which can be analyzed using functional and molecular assays.²⁰ Our central biomarker hypothesis was that CTCs can be used to interrogate AR localization and MTB to determine an association with response in men treated with a taxane.

In the current study (TAXYNERGY; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01718353) identifier: NCT01718353), we prospectively evaluated the benefit of an early switch from docetaxel to cabazitaxel or vice versa using early PSA changes (in the first 12 weeks of therapy) as a predictor of clinical efficacy or therapeutic resistance. In parallel, CTCs were analyzed at the single-cell level, using DTE criteria to assess whether CTC-specific DTE correlated with sensitivity to taxane treatment on an individual basis. The study met its primary objectives by demonstrating a benefit for early taxane switch as evaluated by confirmed PSA responses and an association of response with early changes in AR nuclear localization (ARNL) in CTCs.

PATIENTS AND METHODS

Patient Population and Study Design

TAXYNERGY enrolled chemotherapy-naïve patients with progressive mCRPC and an Eastern Cooperative Oncology Group performance score (ECOG PS) of 0 to 2, with no prior β isotope therapy, whole pelvic radiotherapy, or radiotherapy to > 30% of bone marrow. Patients with neuropathy grade > 2 were excluded. Prior hormonal therapy (including potent CYP17 inhibitors and AR signaling inhibitors) and immunotherapy were allowed.

In this noncomparative randomized study, patients were randomly assigned 2:1 to initiate docetaxel 75 mg/m² or cabazitaxel 25 mg/m² every

3 weeks plus daily prednisone 10 mg. The study was initially designed shortly after the US Food and Drug Administration approval of cabazitaxel, and conservatively, it was decided to have more patients receive docetaxel followed by cabazitaxel (the approved sequence) with the primary analysis in that cohort. With five patients enrolled, the protocol was amended, under the hypothesis that the two taxanes had similar activity in the first-line setting, to reduce the sample size and to pool both random assignment arms in the primary clinical and biomarker analyses while maintaining adequate power. Enrollment continued for 10 months after the amendment up to a total of 63 patients; study data and random assignment remained blinded during this time.

Patients achieving a $\geq 30\%$ PSA decline from baseline by cycle 4 (C4; week 12) continued to receive the same chemotherapy agent, whereas those who did not achieve a $\geq 30\%$ PSA decline were switched to the other taxane (Fig 1A). Patients could also switch taxanes for radiologic progression by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1²¹ in measurable lesions, regardless of PSA change. Switch could only occur at cycle 5 (C5). Treatment continued until disease progression, death, unacceptable toxicity, or withdrawal of consent.

The study was approved by the institutional review board at each participating center and conducted in compliance with guidelines for Good Clinical Practice. Patients provided written informed consent before participation.

Efficacy Assessments

The primary clinical endpoint was PSA response rate, defined as the proportion of patients who achieved a $\geq 50\%$ PSA decrease from baseline, confirmed 3 weeks later,²² whether a treatment switch occurred. Secondary efficacy assessments included progression-free survival (PFS; defined as the time from random assignment to the first of the composite endpoints: PSA, radiographic, or clinical progression or death) and overall survival (OS; defined as the time from random assignment to death). PSA measurements were taken every 3 weeks, and radiologic evaluations (chest, abdomen, and pelvis computed tomography; whole-body bone scan) were performed every 12 weeks until radiologic tumor progression or study cutoff.

The coprimary efficacy endpoint was DTE. CTCs were isolated at specified time points (Fig 1A) using geometrically enhanced differential immunocapture,²⁰ immunostained, and analyzed for CTC-specific biomarkers using multiplex confocal microscopy (Data Supplement). CTCs at baseline (cycle 1 day 1 [C1D1]) were compared with CTCs isolated after 1 week of treatment (cycle 1 day 8 [C1D8]) for percent ARNL (%ARNL) and MTB. %ARNL was determined by quantification of integrated AR staining intensity in the total cell and nucleus areas. MTB was qualitatively assessed by three independent operators for increase compared with C1D1 on a scale of 0 to 3 from no to most MTB increase. Findings were correlated with clinical parameters for all CTC-evaluable patients.

Safety Assessments

Safety assessments included ongoing analysis of adverse events and serious adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events v4.03),²³ vital signs, physical examinations, ECOG PS, and laboratory findings (hematology, serum biochemistry, coagulation, and urinalysis).

Statistical Considerations

Sample size determination was based on a historical PSA response rate of 45.4% from the intent-to-treat population in the TAX327 study.¹ In TAXYNERGY, we reasoned that a 25% relative improvement in PSA response rate to 58% using the early-switch strategy would be clinically meaningful, and an estimate of the response rate with a one-sided 90% CI was calculated. The trial would be considered successful if the lower bound of the one-sided 90% CI did not contain the TAX327 PSA response rate of 45.4% (with 60 patients, the width of the one-sided 90% CI was 8.2%).

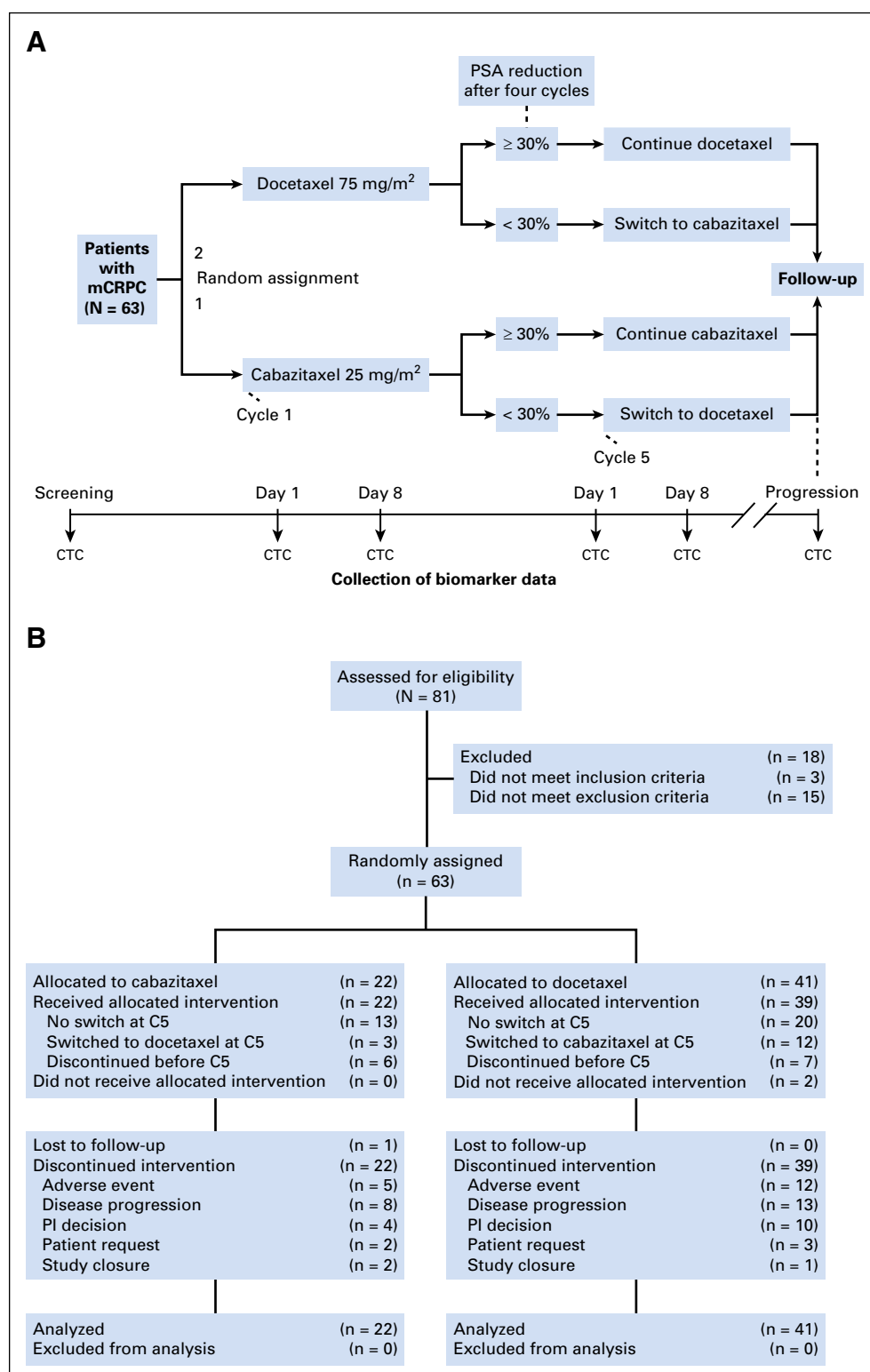


Fig 1. (A) Study design. (B) CONSORT diagram. C5, cycle 5; CTC, circulating tumor cell; mCRPC, metastatic castration-resistant prostate cancer; PI, principal investigator; PSA, prostate-specific antigen.

The main focus of the biomarker analyses was the change between C1D1 and C1D8 in %ARNL and MTB and its association with PSA ($\geq 50\%$) response. Additional exploratory analyses examined other intervals (including change between pretreatment and C5 and PSA decline by $\geq 30\%$). Absolute differences, and differences separated into categories, were examined by analysis of variance and waterfall plots.

Secondary clinical endpoints were analyzed by descriptive statistics and survival techniques. PSA response rates were reported. Time-to-event endpoints (PFS and OS) were evaluated using Kaplan-Meier curves and 95% CIs. All statistical tests were two-sided, with a significance level of $P < .05$. Analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC).

RESULTS

Patient and Treatment Characteristics

Between November 2012 and June 2014, 63 patients were randomly assigned to initial docetaxel ($n = 41$) or cabazitaxel ($n = 22$), and 61 patients received treatment (Fig 1B). Two patients initially randomly assigned to receive docetaxel did not receive treatment as a result of withdrawal of consent.

Baseline patient and disease characteristics are provided in the Data Supplement. Median age was 71 years; most patients had an ECOG PS ≥ 1 (66.7% and 4.8% had ECOG PS of 1 and 2, respectively). Median PSA was 82.30 ng/mL, and 34.9% of patients had visceral metastases. In total, 28 patients (44.4%) received prior treatment with potent AR-targeted therapy. The mean duration of study treatment was 26.1 weeks (median, 27 weeks; range, 3.1 to 60 weeks); the mean number of cycles was 8.4. The most common reasons for treatment discontinuation were disease progression ($n = 21$, 34.4%), adverse event ($n = 17$, 27.9%), and investigator decision ($n = 14$, 23.0%; Data Supplement).

Primary Efficacy EndPoint and PSA Changes From Baseline

The primary endpoint of this study was PSA response rate, defined as the proportion of randomly assigned patients who achieved a confirmed $\geq 50\%$ PSA response during the whole treatment continuum, before treatment switch and after treatment switch, if applicable. Across the entire treatment continuum by intent-to-treat analysis, 35 (55.6%) of 63 patients achieved a $\geq 50\%$ PSA response; 25 patients (39.7%) achieved the response on or before C4, and 10 patients (15.9%) achieved the response after C4. The lower limit of the 90% one-sided CI was 47.5%, which did not overlap with the rate of 45.4% in TAX327.¹ Therefore, the primary clinical endpoint was met. The PSA response rates in men who had and had not received prior potent AR-targeted therapy were 44% (11 of 25 patients) and 68% (24 of 35 patients), respectively ($P = .069$).

Of 61 treated patients, 15 (24.6%) switched treatment after C4 as a result of an early PSA reduction $< 30\%$ ($n = 14$) or radiographic progression ($n = 1$) and were treated with the alternative taxane. Thirty-three patients (54.1%) achieved early $\geq 30\%$ PSA reduction and remained on their initial taxane, and 13 patients (21.3%) discontinued treatment before C5 (Table 1). Of the 15 patients who switched, seven (46.7%) subsequently achieved a PSA response. Changes in PSA from baseline per patient are shown in the Data Supplement.

Secondary Efficacy Endpoints

Median composite PFS was 9.1 months (95% CI, 4.93 to 11.70 months; Fig 2A). Median radiographic PFS and OS were not reached; after a median follow-up of 14 months, $> 50\%$ of patients were still alive (Fig 2B). PSA PFS is shown in the Data Supplement.

Biomarker Analysis: Nuclear AR Localization and Tubulin Bundling in CTCs

Of 60 patients who had PSA assessment, 44 had evaluable CTCs at C1D1, 31 had evaluable CTCs at C1D8, and 25 had evaluable CTCs at both C1D1 and C1D8. This analysis was based on

Table 1. Summary of Patients by Treatment and Taxane Switch (treated population)

Switch Status	No. of Patients (%)		
	All Patients (N = 61)	Cabazitaxel (n = 22)	Docetaxel (n = 39)
No taxane switch	46 (75.4)	19 (86.4)	27 (69.2)
No switch after cycle 4	33 (54.1)	13 (59.1)	20 (51.3)
Switch not applicable*	13 (21.3)	6 (27.3)	7 (17.9)
Taxane switch	15 (24.6)	3 (13.6)	12 (30.8)

*Patients who discontinued treatment before cycle 5.

mechanistic studies showing that taxanes impair ARNL downstream of microtubule stabilization.^{6,7} Therefore, we calculated %ARNL at C1D1 and C1D8 and assessed whether a decrease in %ARNL at C1D8 was associated with PSA response. There were no significant correlations between baseline biomarker parameters and any clinical outcomes (data not shown). Figure 3 shows representative high-resolution images of CTCs captured by geometrically enhanced differential immunocapture with high and low %ARNL. After 1 week of taxane therapy (C1D8), mean %ARNL was significantly lower in patients who subsequently achieved a $\geq 50\%$ PSA reduction at C4 versus those without PSA response (44.0% v 64.1%, respectively; $P = .004$; Data Supplement). PSA responses were more common in patients with %ARNL at C1D8 that was in the lower three quartiles than in patients with %ARNL in the upper quartile (Fig 4A). By C1D8, mean %ARNL decreased by 17.6% in patients with $\geq 50\%$ PSA decrease and increased by 2.3% in patients without a $\geq 50\%$ PSA decrease ($P = .020$). A taxane-induced decrease in mean %ARNL (C1D8 v C1D1) was associated with a higher rate of $\geq 50\%$ PSA decrease (72.7% v 12.5% of patients with no decrease in mean %ARNL; $P = .009$). PSA responses were also more common in patients with decreasing mean %ARNL at C1D8 compared with C1D1 than in men with increasing mean %ARNL (Fig 4B). In exploratory analysis of %ARNL at C5 day 1 to C5 day 8 after taxane switch, mean %ARNL decreased (74.26 at C5 day 1 to 63.84 at C5 day 8; $P = .05$).

At C1D8, mean increase in MTB was numerically higher in patients who achieved an initial $\geq 30\%$ PSA decrease compared with nonresponders, although this did not achieve statistical significance (0.69 v 0.09, respectively; $P = .093$). Taxane-induced increase in mean MTB score trended toward an association with response and was observed in patients who did not require a taxane switch after C4, but this did not achieve statistical significance (0.75 v 0.09 in those who required a switch; $P = .059$; Data Supplement).

Safety

Treatment-emergent adverse events (TEAE) leading to permanent treatment discontinuation were reported in 17 patients (27.9%) and were possibly related to the study drugs in 13 patients (21.3%). Dose modification as a result of a TEAE was reported in 27 patients (44.3%). The most frequently reported TEAEs in all patients were fatigue, diarrhea, and nausea (67.2%, 55.7%, and 41.0% overall, respectively; Table 2).

The most frequent grade 3 or 4 TEAEs were febrile neutropenia and fatigue. There were two deaths as a result of TEAEs, both in docetaxel-treated patients; one death was a result of an

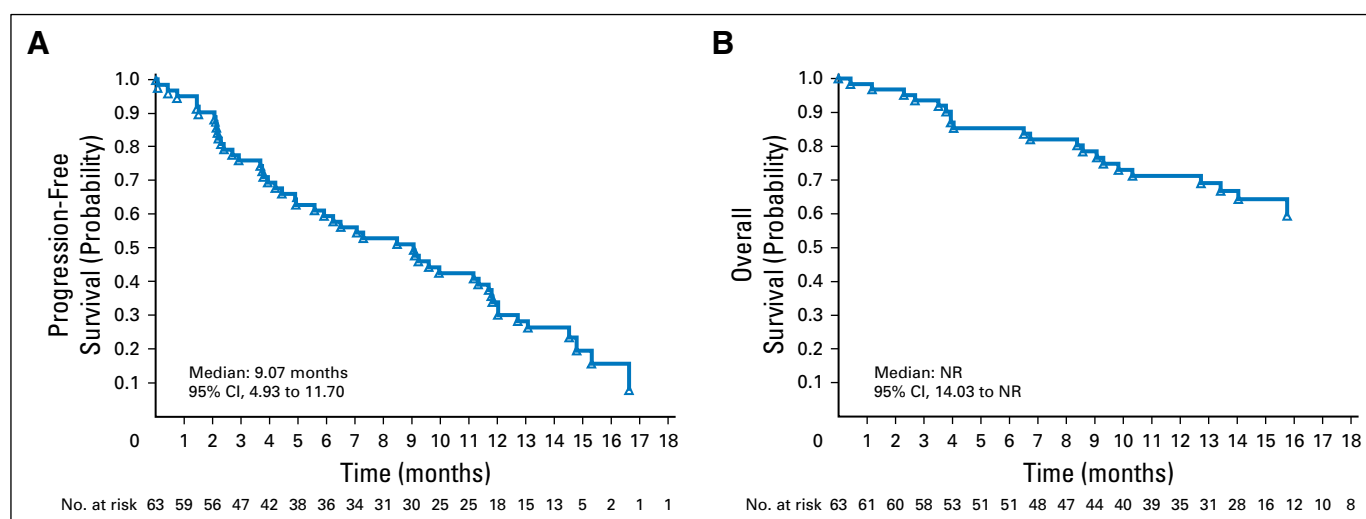


Fig 2. (A) Progression-free survival (all patients). (B) Overall survival (all patients). NR, not reached.

unrelated septic shock, and the other was reported as a possibly related myocardial infarction. Serious adverse events and dose modifications are summarized in the Data Supplement.

DISCUSSION

TAXYNERGY was conducted to test the clinical hypothesis that switching taxane therapy in men who do not achieve an optimal

PSA reduction in the first 12 weeks of therapy may improve clinical outcomes and subvert resistance. Our primary biomarker hypothesis was that ARNL and MTB could be assessed reliably from CTCs and would be associated with outcome in patients treated with taxanes. The confirmed PSA response rate observed using the switch strategy (55.6%) was superior to the prespecified historical control trial (TAX327).¹ Importantly, 46.7% of men who did not achieve a $\geq 30\%$ PSA reduction in the first 12 weeks of treatment subsequently achieved a $\geq 50\%$ PSA response by switching taxane therapy.

In addition, biomarker analyses from CTCs corroborated emerging preclinical data that taxanes may mediate some of their activity in prostate cancer by impairing AR trafficking along the microtubules from the cytoplasm into the nucleus, whereas persistent nuclear AR localization despite taxane therapy may be a marker of primary or early acquired resistance.^{6,7,9} To our knowledge, this is the first prospective trial to report changes in ARNL and MTB in CTCs in patients with prostate cancer receiving taxane therapy, and this trial has demonstrated the feasibility of conducting a biomarker-rich trial across multiple US and Canadian sites. Initial exploratory analyses of %ARNL and MTB in CTCs as a marker of DTE suggest a potential association with sensitivity to taxane therapy. To this end, the totality of the data from TAXYNERGY suggest that although these baseline biomarker parameters are not prognostic for clinical outcomes to chemotherapy, dynamic taxane-induced changes in ARNL (and perhaps MTB) may be indicative of benefit. More specifically, a decrease in nuclear-localized AR (which may be evaluable in CTCs as early as 1 week after therapy initiation) is prognostic for better outcomes. This clinical experience corroborates previous laboratory studies showing that taxanes can inhibit AR nuclear trafficking via stabilization of microtubules.^{6,7,9} How prostate cancer cells manipulate this mechanism of action to resist DTE and the differences between sensitivity to docetaxel versus cabazitaxel have yet to be determined. Interestingly, β -tubulin point mutations have been shown to confer resistance to paclitaxel, but not docetaxel, suggesting that single point mutations may affect one taxane but not others, despite a shared binding site.²⁴⁻²⁶

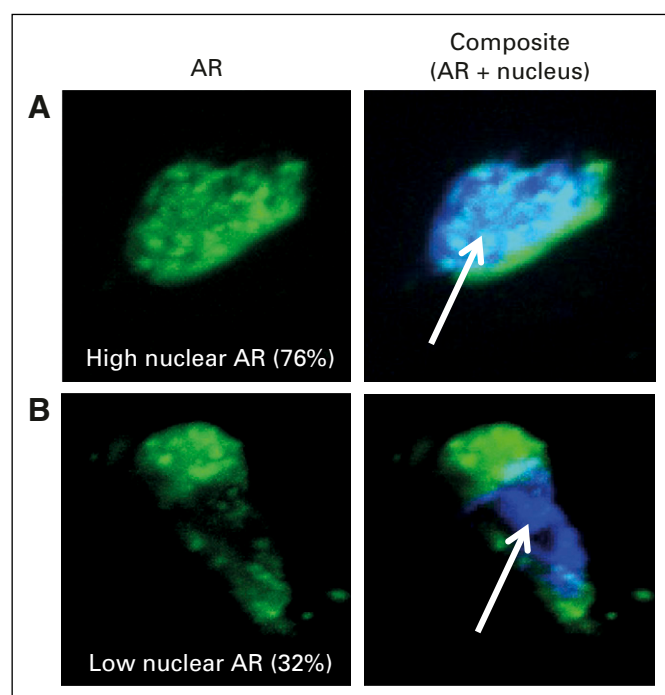


Fig 3. Representative high-resolution images of circulating tumor cells captured by geometrically enhanced differential immunocapture with (A) high and (B) low percent androgen receptor (AR) nuclear localization as assessed by quantitative image analysis. Immunofluorescence staining for AR is indicated in green. 4',6-Diamidino-2-phenylindole staining for DNA (nucleus) is indicated in blue (arrow).

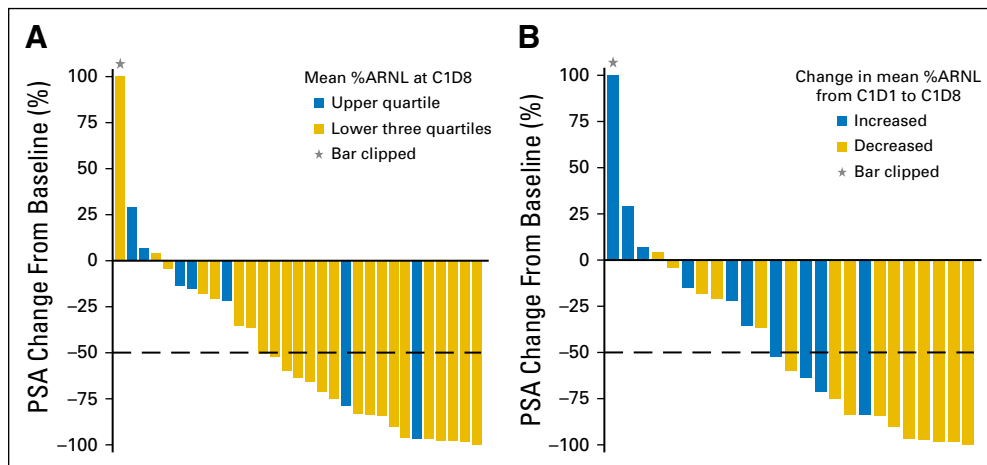


Fig 4. Greatest prostate-specific antigen (PSA) change from baseline at any time on study according to mean percent androgen receptor nuclear localization (%ARNL) at cycle 1 day 8 (C1D8; after 1 week of therapy). (A) Comparison of the lower three quartiles versus the upper quartile of mean %ARNL at C1D8 ($n = 31$); PSA $\geq 50\%$ decrease from baseline was more common in patients with %ARNL in the lower three quartiles (71%) than in patients with %ARNL in the upper quartile (29%). (B) Comparison of increase versus decrease in %ARNL from cycle 1 day 1 (C1D1) to C1D8 ($n = 25$); PSA change from baseline was 40% in patients with increased mean %ARNL compared with 67% in patients with decreased mean %ARNL. Thirty-one patients had PSA change and evaluable circulating tumor cells (CTCs) at C1D8; 25 patients had PSA change and evaluable CTCs at both C1D1 and C1D8.

There are several clinical implications of this study. First, although this study is not sufficient to change the standard of care among patients with mCRPC receiving taxane therapy, it suggests that a treatment switch from one taxane to the other may be worthy of further investigation in patients who do not achieve a $\geq 30\%$ PSA reduction within the first 12 weeks. Importantly, prior studies have shown that men who do not achieve a 30% PSA decline by week 12 of treatment have a poorer survival with docetaxel and cabazitaxel than those who do.^{27,28} Second, it suggests that changes

in CTC-specific ARNL observed as early as 1 week after therapy initiation may be a potentially more sensitive and specific biomarker of subsequent clinical response than 12-week PSA changes. Future prospective studies should evaluate whether switching taxane therapy early on the basis of a CTC biomarker may improve outcomes compared with switching therapy on the basis of PSA trends (or not switching therapy at all).

This study has several limitations. First, on the basis of its design and relatively small sample size, it used an assumption that

Table 2. Summary of Key TEAEs

TEAE	All Grades, No. of Patients (%)			Grade 3 or 4, No. of Patients (%)		
	Cabazitaxel Throughout ($n = 19$)	Docetaxel Throughout ($n = 27$)	Both Drugs ($n = 15$)	Cabazitaxel Throughout ($n = 19$)	Docetaxel Throughout ($n = 27$)	Both Drugs ($n = 15$)
Key TEAEs						
Diarrhea	12 (63.2)	13 (48.1)	9 (60.0)	1 (5.3)	0	0
Neuropathy, peripheral	6 (31.6)	9 (33.3)	3 (20.0)	0	0	2 (13.3)
Febrile neutropenia	3 (15.8)	5 (18.5)	0	3 (15.8)	4 (14.8)	0
Dysgeusia	2 (10.5)	4 (14.8)	3 (20.0)	0	0	0
Paresthesia	2 (10.5)	3 (11.1)	3 (20.0)	0	0	0
Asthenia	0	4 (14.8)	1 (6.7)	0	1 (3.7)	0
Other TEAEs in $\geq 10\%$ of patients						
Fatigue	13 (68.4)	18 (66.7)	10 (66.7)	3 (15.8)	2 (7.4)	3 (20.0)
Nausea	10 (52.6)	8 (29.6)	7 (46.7)	0	0	1 (6.7)
Alopecia	5 (26.3)	9 (33.3)	5 (33.3)	0	0	0
Decreased appetite	4 (21.1)	8 (29.6)	4 (26.7)	1 (5.3)	0	1 (6.7)
Abdominal pain	4 (21.1)	7 (25.9)	4 (26.7)	0	0	0
Constipation	6 (31.6)	3 (11.1)	5 (33.3)	0	0	0
Vomiting	7 (36.8)	3 (11.1)	4 (26.7)	0	0	0
Edema, peripheral	3 (15.8)	7 (25.9)	4 (26.7)	0	0	0
Dyspepsia	3 (15.8)	3 (11.1)	3 (20.0)	0	0	0
Dizziness	3 (15.8)	3 (11.1)	3 (20.0)	0	0	0
Laboratory parameter						
Anemia	18 (94.7)	23 (85.2)	14 (93.3)	1 (5.3)	1 (3.7)	0
Thrombocytopenia	5 (26.3)	3 (11.1)	3 (20.0)	0	0	0
Leukopenia	4 (21.1)	4 (14.8)	4 (26.7)	2 (10.5)	1 (3.7)	0
Neutropenia	3 (15.8)	2 (7.4)	1 (6.7)	2 (10.5)	1 (3.7)	0

Abbreviation: TEAE, treatment-emergent adverse event.

the activity of docetaxel and cabazitaxel is similar in chemotherapy-naïve patients with mCRPC. The limited sample size affected follow-up biomarker time points even more profoundly, especially with respect to paired samples. For example, not all patients with evaluable baseline CTCs had paired samples available at C1D8, possibly as a result of elimination of tumor cells from the circulation by effective chemotherapy. Second, the length of follow-up was relatively short, and we were not able to assess radiographic PFS or OS reliably or determine whether any biomarker signature was associated with improved survival. Third, the trial was not designed to definitively answer the question of whether a taxane switch (based on either PSA criteria or CTC-derived ARNL criteria) was superior with respect to OS than no switch at all. Such questions should form the basis for future studies randomly assigning patients to a switch strategy versus no switch. Finally, our ability to draw firm conclusions about the value of the early-switch strategy was limited by the small number of patients who underwent a taxane switch ($n = 15$), as a result of the significant activity of both agents in the chemotherapy-naïve mCRPC setting. Therefore, the study was unable to definitively prove that the taxane switch was responsible for subsequent PSA responses in those switching therapy or that biomarker modulation after switch induced those PSA responses.

All patients in the safety population experienced at least one TEAE. Grade 3 or 4 TEAEs were reported in 51% of patients; of these, the most frequently reported were febrile neutropenia and fatigue. No grade 3 or 4 febrile neutropenia events were reported in patients who switched taxane, although it should be noted that there was only a small number of patients in this subgroup. In general, the safety profiles of cabazitaxel and docetaxel were consistent with previous studies, and no new safety concerns were identified.

In conclusion, to our knowledge, this is the first prospective study to evaluate the benefit of an early switch in taxane therapy on

the basis of the absence of a $\geq 30\%$ PSA response after 12 weeks of therapy, and it suggests improved outcomes compared with historical controls with this approach. To our knowledge, it is also the first study to incorporate real-time on-treatment measurements of %ARNL and MTB from CTCs, indicating that these early measures may be associated with benefit in men treated with taxanes. Further dedicated prospective randomized trials focusing on a taxane switch using integral biomarkers are warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Supported by Sanofi. This work was also partially supported by the National Institutes of Health (NIH) Grants R01 CA177165 (to PG) and R01 CA179100 (to PG), and by the Clinical and Translational Science Center at Weill Cornell NIH/NCATS grant UL1TR00457 (to GG).

Prior Presentation

Presented, in part, at the 2015 European Cancer Conference, Vienna, Austria, September 25-29, 2015; 52nd Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 3-7, 2016; and 2017 Genitourinary Cancers Symposium, Orlando, FL, February 16-18, 2017.



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized, Noncomparative, Phase II Trial of Early Switch From Docetaxel to Cabazitaxel or Vice Versa, With Integrated Biomarker Analysis, in Men With Chemotherapy-Naïve, Metastatic, Castration-Resistant Prostate Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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Acknowledgment

Editorial support was provided by Olga Ucar and Paul Scutt of MediTech Media, funded by Sanofi Genzyme.